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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,155	10/14/2004	Oliver Schadt	MERCK-2932	9151

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EXAMINER	
GRAZIER, NYEEMAH	
ART UNIT	**PAPER NUMBER**
1626	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,155	SCHADT ET AL.	
	Examiner	Art Unit	
	Nyeemah Grazier	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-16 and 18-22* is/are pending in the application.

4a) Of the above claim(s) *18-20 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,7 and 9-16* is/are rejected.

7)☒ Claim(s) *5 and 21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

FINAL REJECTION

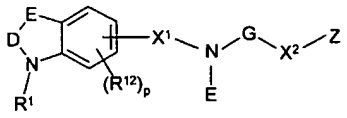
I. ACTION SUMMARY

The Amendments to the Claims and Remarks submitted to the Office on October 10, 2006 has been fully considered and will be the basis of the following Action.

II. RESPONSE TO AMENDMENTS

A. *Restriction/Election*

Applicant's arguments, see Remarks, filed October 10, 2006, with respect to the restriction and election of specie requirement have been fully considered and are not persuasive because there is not a core that contributes over the art. First, the claim is drawn to the following fused benzyl ring:



For all the reasons stated in the Lack of Unity of Invention Letter mailed on or about May 8, 2006, unity of invention is lacking. Thus, the restriction is still deemed Final.

B. 35 U.S.C. §101/§112 Rejection

Applicant's arguments, see Remarks, filed October 10, 2006, with respect to the "use" claims and the terms "derivative" and the range within a range language in claims 2 and 3. Rejections have been fully considered and are persuasive.

Claims 12-16 have been amended by deleting "Use of" and inserting "A method for." Thus, the rejection has been obviated by the amendment.

Claims 1-4 were rejected under 112, 2nd paragraph. The rejection is obviated by the amendment.

Claims 2 and 3 were rejected under 112, 2nd paragraph. However, the rejection is obviated by the amendment.

C. 35 U.S.C. §102 Rejection

Applicant's argument, see Remarks, filed October 10, 2006, with respect to the 102(b) rejection of claims 1 and 3. The rejection has been obviated in light of the amendments.

D. Claim Objections

Claims 1-4 were objected to for containing non-elected subject matter. The objection is maintained because the claims as amended contain non-elected subject matter. To obviated the objection, the Applicant should amend the claims to read on the elected subject matter as stated in the Action dated May8, 2006. See pp. 3-4.

Claims 8-11 were objected as substantial duplicates. The objection is obviated because the claims have been canceled or amended. Claim 8 has been canceled and claims 9-11 have been amended and now claim a different subject matter, namely, method of treatment claims. The objection has been obviated.

Claims 2-17 have bee objected to as being dependent on a rejected/objected based claim. The objection is maintained.

III. REJECTION

Applicant's amendment necessitated the new ground of rejection presented in this Office Action. Accordingly, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) that forms the basis for all obviousness rejections set forth in this Office action:

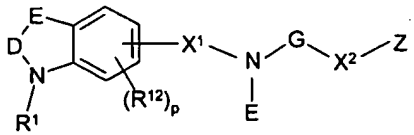
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Graham v. John Deere Co. set forth the factual inquiries necessary to determine obviousness under 35 U.S.C. §103(a). *See Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Specifically, the analysis must employ the following factual inquiries:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 6, 7, 12-16, are rejected under 35 U.S.C. § 103(a) as being obvious *Peglion et al.*, US 6,399,616 B1.

The instant invention is drawn to the compounds and composition of formula (I) and the method of making and using same, where formula (I) is:



The applicant has elected a provisional species as the formula (I) encompasses a vast amount of compounds. Thus, the relevant subject matter are the compounds of formula (I) wherein:

R^1, A, D-E, Het, Ar, Hal, w, n, g and m are recited in claim 1;

X^1 is (CHR7)g;

E and G together form a saturated 1,4-diazine ring wherein the additional nitrogen is linked directly to variable Z;

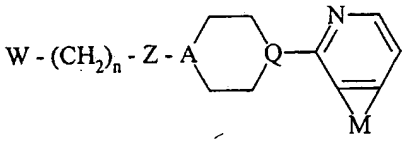
X^2 is a bond; and

Z represents an aromatic heterocyclic ring containing 1 to 4 heteroatoms selected independently from N, O, and S. See, Action, Section IV. B., pp. 3-4 dated May 8, 2006.

The compounds and compositions allegedly **exhibit activity on the central nervous system, especially 5HT reuptake-inhibiting and $5HT_x$-agonistic and/or antagonistic actions.** Specification, p. 6, ll. 20-23.

The Scope and Content of the Prior Art (MPEP §2141.01)

The prior art of reference (" the '616 patent") teaches pyridine compounds and compositions of formula (I) and there uses for the "**treatment of disorders resulting from problems of which the cause lies in the central serotonergic system an which are known to be mediated in the reuptake of serotonin and or at the level of 5-HT_{1A} receptors.**" US 6,399,616 B1, col. 1, ll. 4-11. Formula (I) of the '616 patent has the following formula:



The Difference Between the Prior Art and the Claims (MPEP §2141.02)

The instant invention and the invention taught in the '616 patent are both drawn to compounds useful for the treatment of disorders resulting from problems of which the cause lies in the central serotonergic system an which are known to be mediated in the reuptake of serotonin and or at the level of 5-HT_{1A} receptors. Both the instant invention and the '616 patent consist of a 1,4-diazine moiety that is directly bonded to a heterocyclic polycyclic ring which is N-linked on one end of the scaffold and s N-linked alkyl substituted by indolyl ring on the other side of the diazine ring. The difference between the instant invention and the '616 patent is in scope because they are each drawn to a different formula. *See above*. Particularly, the instant invention has been amended by deleting "H" as a representative of R^2, R^3, R^4 and R^5. However, R^2, R^3, R^4 and R^5 may represent "methyl" for example. Thus, the difference is a methyl versus a hydrogen atom.

Furthermore, the '616 patent teaches compounds of formula (I) wherein "W" represents group "Y" which is drawn to an indole which may be optionally substituted by halogen, trihaloalkyl, nitro, and linear and branched (C_1-C_6) alkyl groups. These are the same groups defined in "D-E."

Resolving Level of Ordinary Skill in the Pertinent Art

The level of ordinary skill in the pertinent art is high as the invention is drawn to compounds having pharmaceutical activity. The motivation to make claimed compound derives from the expectation that structurally similar compounds are generally expected to have similar properties and have similar utilities. In re Gyurik, 596 F. 2d 1012, 201 USPQ 552 (CCPA 1979).

Prima Facie Obviousness-The Rational and Motivation (MPEP §2142-2413)

It is well established that consideration of a reference is not limited to the preferred embodiments or working examples, but extends to the entire disclosure for what it fairly teaches, when viewed in light of the admitted knowledge in the art, to a person of ordinary skill in the art. In re Boe, 148 USPQ 507 (CCPA 1966). For an invention to be obvious, two things must be found in the prior art: 1) the suggestion of the invention, and 2) the expectation of success. In re Vaeck, 20 USPQ.2d 1438, 1441 (Fed. Cir. 1991).

It is well established that the substitution of methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results. *In re* Woods, 582 F.2d 638, 199 USPQ 137 (CCPA 1978). The prima facie case for obviousness is derived from the preferred teaching of the references, which in the instant case, would suggest the instant invention. Furthermore, the reference specifically teaches a species of the general formula (I) whereby the only difference between in the instant invention and the prior art is the alkyl (i.e. methyl) substitution on the indole ring of the instant invention.

Additionally, the '616 patent teaches "advantageous" embodiments, for instance, wherein W is preferably 2,3-dihydro-1-benzofuran-5-yl, Z preferably represents a single bond and n preferably represents 2 or 3.

The expectation of success is derived from the prior art of reference because the publication discloses species drawn to 4-{4-[2-(1H-Indol-5-yl)ethyl]-1-piperazinyl}furo[3,2-c]pyridine. Additionally, the specification teaches how to make the compounds and disclose protocol used to test the compounds for it inhibitory effects. Thus, although the claims are not identical, the prior art of reference suggests the instant invention.

The Applicant may obviate the rejection by amending group "Z."

A. Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not sufficiently described in the specification in such a way as to enable on skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention without undue experimentation.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The relevant factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph have been set forth in In re Wands. See In re Wands, 8 USPQ.2d 1400 (1988). The factors are as follows:

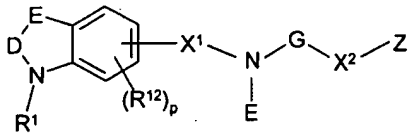
1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

Claims 9-11 are rejected (1) "a method for modulating" does not recite a substantial utility especially since the invention is drawn to a pharmaceutical product. (2)Also, the claims recite "modulating" which includes antagonist and agonist activity. How is the activity modulated and what diseases are treated by the process?

Claims 12-16 are rejected because the claims asserts a method of "preventing" diseases such as "Alzheimer's diseases" and "Parkinson's disease" for example. Also, the claims seeks to treat all or any 5HT-mediated disease without sufficient support in the Specification.

The Nature of the Invention

The instant invention is drawn to the compounds and composition of formula (I) and the method of making and using same, where formula (I) is:



The applicant has elected a provisional species as the formula (I) encompasses a vast amount of compounds. Thus, the relevant subject matter are the compounds of formula (I) wherein:

R^1, A, D-E, Het, Ar, Hal, w, n, g and m are recited in claim 1;

X^1 is (CHR7)g;

E and G together form a saturated 1,4-diazine ring wherein the additional nitrogen is linked directly to variable Z;

X^2 is a bond; and

Z represents an aromatic heterocyclic ring containing 1 to 4 heteroatoms selected independently from N, O, and S. See, Action, Section IV. B., pp. 3-4 dated May 8, 2006.

The compounds and compositions allegedly **exhibit activity on the central nervous system, especially 5HT reuptake-inhibiting and $5HT_x$-agonistic and/or antagonistic actions.** Specification, p. 6, ll. 20-23.

However, there is a no support in the specification that the prevention of the diseases claimed are predictive of the utility asserted, especially absent pharmacological data. Also, there are no known agents that treat Alzheimer's and neurodegenerative diseases all inclusively. Furthermore, said rejected claims fail to state the required dosage that is administered. Thus, said rejected claims and the dependent claims lack enablement under 35 U.S.C. 112, first paragraph

The Level of Skill in the Art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit

from this activity. For example, the treatment of Alzheimer's disease and neurodegenerative diseases is highly unpredictable.

The Predictability or Lack Thereof in the Art

Because of high level of unpredictability associated with "prevention" of certain diseases such as allergies, a greater amount of evidentiary support is needed to satisfy the requirement of 35 U.S.C 112, first paragraph. Additionally, formula (I) of the instant invention is drawn to potentially 500+ distinct compounds. It is noted tat the pharmaceutical art is unpredictable and requires the embodiments to be individually assessed for physiological activity. Thus, the more unpredictable the art, more information in support of the invention is required to satisfy the statute. See In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970).

The Amount of Direction or Guidance Present

In the instant case, Applicants recite a method modulating activity, a method for preventing diseases and a method of treating any disease that is a 5HT-mediated disease. However, the applicant has not demonstrated sufficient guidance provided in the form of profiles, ratios of the active agents or references to same in the prior art to provide a skilled artisan with sufficient guidance to practice the instant of Alzheimer's and neurodegenerative diseases claimed.

The Presence or Absence of Working Examples

Enablement for a single compound cannot provide enablement for the breath of claims sought in arts which are unpredictable. Ex parte Hitzeman, 9 USPQ.2d 1821 (BPAI 1987) (a single embodiment may provide broad enablement in cases involving predictable factors, but more is required in cases involving unpredictable factors, such as chemical or physiological activity); In re Shokal, 113 USPQ283, 285 (CCPA 1957) (a single species is seldom, if ever, sufficient to support a generic claim); In re Langer, 183 USPQ 288 (CCPA 1974) (proof of utility for the preferred species does not necessarily establish the utility of the remaining members of the genus); Ex parte Lanham, 135 USPQ 106 (POBA 1961) (biological activity of chemicals is

notoriously unpredictable). Thus, the specification fails to bridge the gap between the classes of compounds (i.e. 6 membered hetrocyclic compounds, 5 member heterocyclic compounds and the like) and there activity as 5HT modulator wherein in the method may prevent Alzheimer's disease.

The Breadth of the Claims

The claims recite very broadly, "a method for modulating" without reciting a substantial utility especially since the invention is drawn to a pharmaceutical product. Also, the claims recite "modulating" without specifying how is the activity modulated and what diseases are treated by the process? Claims 12-16, for example asserts a method of "preventing" diseases such as "Alzheimer's diseases" and "Parkinson's disease" for example. Also, the claims seek to treat all or any 5HT-mediated disease without sufficient support in the Specification. Said claims also treat unrelated diseases/conditions such as paid and Alzheimer's.

The Quantity of Experimentation Needed

Based on the unpredictable nature of the invention and the state of the prior art and the breadth of the claims, one of ordinary skill in the art would be burdened with undue "experimentation study" to determine whether the claimed compounds would prevent diseases ***unrelated diseases*** such as pain and Alzhiemer's disease. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ.2d 1001 (stating that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable").

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which compounds would prevent, for example, allergic diseases by the method encompassed in the instant claims, with no assurance of success.

In sum, to overcome this rejection the Examiner suggests that Applicant cancel claims 9-11, combine claims 12-15, delete the term "preventing," list only the related disease that have support in the specification, and state the effective dosage required and state to whom or to what (a human, etc.) the dosage is administered.

IV. OBJECTIONS

Claim 13 is objected to because claim 13 has improper format, namely, claim 13 should recite "wherein said disease is selected from a group consisting of" and NOT "Comprising."

New claim 21 is objected to because said claim contains non-elected subject matter.

V. Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nyeemah Grazier whose telephone number is (571) 272-8781. The examiner can normally be reached on Monday through Thursday and every other Friday from 8:30 a.m. - 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane, can be reached on (571).272 - 0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Very truly yours,

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